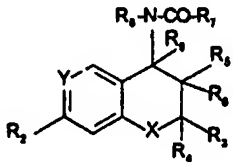




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/EP98/08156 <b>(22) International Filing Date:</b> 14 December 1998 (14.12.98) <b>(30) Priority Data:</b> 9726543.3                      16 December 1997 (16.12.97)    GB <b>(71) Applicant (for all designated States except US):</b> SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> DUMPLETON, David, Robert [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). HOLLAND, Simon, Joseph [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). KNIGHT, Wendy, Anne [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). LEONARD, Graham, Stanley [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).		<b>(74) Agent:</b> WEST, Vivien; SmithKline Beecham, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB). <b>(81) Designated States:</b> AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> PHARMACEUTICAL COMPOSITIONS CONTAINING MICRONIZED BICYCLIC DRUGS <div style="text-align: center;">  <div style="margin-left: 100px;">(1)</div> </div> <b>(57) Abstract</b> <p>A pharmaceutical composition comprising a compound of formula (I) in particulate form, said composition having a particle size distribution such that the median value of the volume mean diameter is within the range of from 350 to 700 nm.</p>		

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## PHARMACEUTICAL COMPOSITIONS CONTAINING MICRONIZED BICYCLIC DRUGS

This invention is concerned with novel compositions of compounds having therapeutic activity in particulate form, especially particulate compositions of sparingly water soluble compounds, with enhanced bio-availability; and to the use of such compositions in therapy.

EP-A-0 126 311 and EP-A-0 139 992 disclose benzopyran derivatives which have anti-hypertensive activity. WO 92/22293, WO 94/13657 and WO 95/34545 disclose that the benzopyran compounds also have anxiolytic and anticonvulsant activity and disclose further benzopyran derivatives and related pyridopyran derivatives having similar activities. Unpublished International Patent Application No PCT/EP97/05168 discloses additional utilities for these compounds, including the treatment of neuropathic pain.

It is known to subject pharmaceutically active compounds to milling procedures to obtain a particle size appropriate for tablet formation and for other formulation types. Air jet milling and fluid energy milling (micronising) have been favoured because of the reduced risk from introducing contamination from mill materials. However, wet milling processes have been proposed for preparation of finely divided particles for pharmaceutical use, for example US-A-4 540 602 and EP-A-0 499 299. The latter discloses a wet milling procedure to produce particles of a crystalline drug substance having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 400 nm. This particulate composition is said to provide improved bioavailability for poorly water soluble compounds.

The present invention is based on the finding that the benzopyran and pyridopyran compounds mentioned above have enhanced bio-availability in certain compositions of controlled particle size. This invention also provides a method of producing such compositions in a reproducible manner.

According to the present invention there is provided a composition comprising a compound of Formula I or Formula II below in particulate form, having a particle size distribution such that the median value of the volume mean diameter is within the range of from 350 to 700 nm.

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Compounds used in this invention are as follows:



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either Y is N and R<sub>2</sub> is hydrogen, or Y is C-R<sub>1</sub>

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is nitro, cyano or C<sub>1-3</sub> alkylcarbonyl and the other is methoxy or amino optionally substituted by one or two C<sub>1-6</sub> alkyl or by C<sub>2-7</sub> alkanoyl;

one of R<sub>3</sub> and R<sub>4</sub> is hydrogen or C<sub>1-4</sub> alkyl and the other is C<sub>1-4</sub> alkyl or R<sub>3</sub> and R<sub>4</sub> together are C<sub>2-5</sub> polymethylene;

R<sub>5</sub> is C<sub>1-6</sub> alkylcarbonyloxy, benzyloxy, ONO<sub>2</sub>, benzyloxy, phenyloxy or C<sub>1-6</sub> alkoxy and R<sub>6</sub> and R<sub>9</sub> are hydrogen or R<sub>5</sub> is hydroxy and R<sub>6</sub> is hydrogen or C<sub>1-2</sub> alkyl and R<sub>9</sub> is hydrogen;

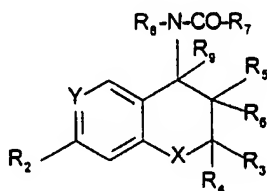
R<sub>7</sub> is fluorophenyl;

R<sub>8</sub> is hydrogen or C<sub>1-6</sub> alkyl;

the R<sub>8</sub>-N-CO-R<sub>7</sub> group being *trans* to the R<sub>5</sub> group;

and X is oxygen or NR<sub>10</sub> where R<sub>10</sub> is hydrogen or C<sub>1-6</sub> alkyl;

and



Formula II

wherein:

either Y is N and R<sub>2</sub> is hydrogen, or Y is C-R<sub>1</sub>

where:

either one of R<sub>1</sub> and R<sub>2</sub> is hydrogen and the other is selected from the class of hydrogen, C<sub>3-8</sub> cycloalkyl, C<sub>1-6</sub> alkyl optionally interrupted by oxygen or substituted by hydroxy, C<sub>1-6</sub> alkoxy or substituted aminocarbonyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxycarbonyl, C<sub>1-6</sub> alkylcarbonyloxy, C<sub>1-6</sub> alkoxy, nitro, cyano, halo, trifluoromethyl, CF<sub>3</sub>S, or a group CF<sub>3</sub>-A-, where A is -CF<sub>2</sub>-, -CO-, -CH<sub>2</sub>-, CH(OH), SO<sub>2</sub>, SO, CH<sub>2</sub>-O, or CONH, or a group CF<sub>2</sub>H-A'- where A' is oxygen, sulphur, SO, SO<sub>2</sub>, CF<sub>2</sub> or CFH; trifluoromethoxy, C<sub>1-6</sub> alkylsulphinyl, perfluoro C<sub>2-6</sub> alkylsulphonyl, C<sub>1-6</sub> alkylsulphonyl, C<sub>1-6</sub> alkoxysulphinyl, C<sub>1-6</sub> alkoxysulphonyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, phosphono, arylcarbonyloxy,

- heteroarylcarbonyloxy, arylsulphinyl, heteroarylsulphinyl, arylsulphonyl, heteroarylsulphonyl in which any aromatic moiety is optionally substituted, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkoxy carbonylamino, C<sub>1-6</sub> alkyl-thiocarbonyl, C<sub>1-6</sub> alkoxy-thiocarbonyl, C<sub>1-6</sub> alkyl-thiocarbonyloxy, 1-mercapto C<sub>2-7</sub> alkyl, formyl, or
- 5 aminosulphinyl, aminosulphonyl or aminocarbonyl, any amino moiety being optionally substituted by one or two C<sub>1-6</sub> alkyl groups, or C<sub>1-6</sub> alkylsulphinylamino, C<sub>1-6</sub> alkylsulphonylamino, C<sub>1-6</sub> alkoxy sulphinylamino or C<sub>1-6</sub> alkoxy sulphonylamino, or ethylenyl terminally substituted by C<sub>1-6</sub> alkylcarbonyl, nitro or cyano, or -C(C<sub>1-6</sub> alkyl)NOH or -C(C<sub>1-6</sub> alkyl)NNH<sub>2</sub>, or one of R<sub>1</sub> and R<sub>2</sub>
- 10 is nitro, cyano or C<sub>1-3</sub> alkylcarbonyl and the other is methoxy or amino optionally substituted by one or two C<sub>1-6</sub> alkyl or by C<sub>2-7</sub> alkanoyl; or R<sub>1</sub> and R<sub>2</sub> together are - (CH<sub>2</sub>)<sub>4</sub>- or -CH = CH-CH = CH-, or form an optionally substituted triazole or oxadiazole ring;
- 15 one of R<sub>3</sub> and R<sub>4</sub> is hydrogen or C<sub>1-4</sub> alkyl and the other is C<sub>1-4</sub> alkyl, CF<sub>3</sub> or CH<sub>2</sub> X<sup>a</sup> where X<sup>a</sup> is fluoro, chloro, bromo, iodo, C<sub>1-4</sub> alkoxy, hydroxy, C<sub>1-4</sub> alkylcarbonyloxy, -S-C<sub>1-4</sub> alkyl, nitro, amino optionally substituted by one or two C<sub>1-4</sub> alkyl groups; cyano or C<sub>1-4</sub> alkoxy carbonyl or R<sub>3</sub> and R<sub>4</sub> together are C<sub>2-5</sub> polymethylene optionally substituted by C<sub>1-4</sub> alkyl;
- 20 R<sub>5</sub> is C<sub>1-6</sub> alkylcarbonyloxy, benzoyloxy, ONO<sub>2</sub>, benzyloxy, phenyloxy or C<sub>1-6</sub> alkoxy and R<sub>6</sub> and R<sub>9</sub> are hydrogen or R<sub>5</sub> is hydroxy and R<sub>6</sub> is hydrogen or C<sub>1-2</sub> alkyl and R<sub>9</sub> is hydrogen;
- 25 R<sub>7</sub> is heteroaryl or phenyl; both of which are optionally substituted one or more times independently with a group or atom selected from chloro, fluoro, bromo, iodo, nitro, amino optionally substituted once or twice by C<sub>1-4</sub> alkyl, cyano, azido, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, trifluoromethoxy and trifluoromethyl;
- 30 R<sub>8</sub> is hydrogen; C<sub>1-6</sub> alkyl, OR<sub>9</sub> or NHCOR<sub>10</sub> wherein R<sub>9</sub> is hydrogen, C<sub>1-6</sub> alkyl, formyl, C<sub>1-6</sub> alkanoyl, aroyl or aryl-C<sub>1-6</sub> alkyl and R<sub>10</sub> is hydrogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, mono or di C<sub>1-6</sub> alkyl amino, amino, amino-C<sub>1-6</sub> alkyl, hydroxy-C<sub>1-6</sub> alkyl, halo-C<sub>1-6</sub> alkyl, C<sub>1-6</sub> acyloxy-C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy carbonyl-C<sub>1-6</sub>-alkyl, aryl or heteroaryl;
- 35 the R<sub>8</sub>-N-CO-R<sub>7</sub> group being *cis* to the R<sub>5</sub> group;

and X is oxygen or NR<sub>10</sub> where R<sub>10</sub> is hydrogen or C<sub>1-6</sub> alkyl.

Compounds within the scope of Formula I and II are disclosed in EP-A-0 139 992,  
5 EP-A-0 126 311, WO 92/22293, WO 94/13657 and WO 95/34545. Reference is  
directed to these publications for information on the preparation and use of these  
compounds, on preferred substituents and substitution patterns, and on suitable  
individual compounds and their preparation.

10 Preferred compounds for use in this invention are *trans*-6-acetyl-4S-(4-  
fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-3R-ol  
hereinafter Compound 1 (for preparation see Example 20 of WO 92/22293); and *cis*-  
6-acetyl-4S-(3-chloro-4-fluorobenzoylamino)-3,4-dihydro-2,2-dimethyl-2H-1-  
benzopyran-3S-ol hereinafter Compound 2 (for preparation see Example 17 of  
15 WO95/34545); and *trans*-6-acetyl-4S-(3,5-difluorobenzoylamino)-3,4-dihydro-2,2-  
dimethyl-2H-1-benzopyran-3R-ol (for preparation see Example 4 of WO95/34545).

The compounds used in this invention have a very low solubility in water. For  
example, Compound 1 has an aqueous solubility of 0.008 mg/ml, which is "virtually  
20 insoluble" under the USP classification.

The above-listed compounds may be used in the form of pharmaceutically acceptable  
solvates, especially hydrates. Before milling they may be in crystalline or amorphous  
form.

25 The compositions of this invention are most suitably prepared by wet milling  
compounds of Formula I and Formula II as an aqueous dispersion. For small scale  
processing the wet milling is preferably carried out using a two chamber bead mill with  
circulation of product between the chambers. To reduce contamination from mill  
30 materials, the milling medium is preferably ceramic beads of rare earth oxides and is  
carried out in chambers lined with or constructed from an abrasion-resistant polymer  
material such as nylon. For effective milling, the beads in one chamber are of a smaller  
diameter than the beads in the other chamber; effective results are obtainable with beads  
of 1.25 mm in one chamber and beads of 0.4 mm in the other chamber. The milling  
35 beads are preferably zirconia beads, especially beads made from yttria-stabilized  
zirconia powder. For larger scale processing a 5 chamber bead mill can be utilised. The

product is processed in one pass through one, two, three, four or all five of the mills. For effective milling, the beads in the first chamber are between 0.65mm and 1.25mm. Beads in subsequent chambers are smaller than or of a similar size to the previous mill

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To assist in further processing, that is preparation of pharmaceutical formulations for therapeutic use, such as tablets, injectable dispersions, etc., the wet milling of compounds of Formula I and Formula II preferably takes place in an aqueous medium including one or more excipients such as a soluble carrier suitable for spray drying, a  
10 surfactant to maintain the particles in suspension, and an anti-agglomeration agent effective after administration of a pharmaceutical formulation to a patient. An especially suitable excipient for spray-drying is mannitol but other carbohydrates such as sorbitol, lactose, lactitol and xylitol and starch may be used as carrier. Preferably sodium lauryl sulphate is used as surfactant, and cellulosic thickening agents such as  
15 hydroxypropyl methyl cellulose or hydroxyethyl cellulose may be used as anti-agglomeration agents.

In the aqueous medium to be subjected to the milling, the compound of Formula I or II may be present from about 10 to about 30% w/w. At 30% w/w and above there may be  
20 difficulties in maintaining a suspension of the compound of Formula I or II during milling. In practice, 20% w/w provides an effective compromise between the desire for a high throughput and short milling times.

The amount of the soluble carrier may vary from about 4 to about 15% w/w of the  
25 composition to be milled. Preferably the amount of the soluble carrier does not exceed 50% by weight of the amount of compound of Formula I or II to be processed. For a compound loading of about 20% w/w, an amount of soluble carrier from about 4 to 10% has been found to be effective and an amount of about 5% w/w is preferred.

30 The amount of surfactant may be varied from about 0.1 to about 0.4% w/w of the aqueous medium. Preferably it is present at about 1% by weight of the compound to be processed.

The amount of the anti-agglomeration agent is typically from about 1% w/w to about  
35 2% w/w of the aqueous medium. An amount of about 1.5% w/w is preferred.



The particles of the compounds of Formula I and Formula II are preferably present as a monomodal distribution, typically with no more than 10% of the particles having a volume diameter of 280 nm or below, and no less than 90% of the particles having a volume diameter of 2000 nm or below.

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In a preferred embodiment of the invention, the median volume diameter is in the range of 400 to 600 nm, especially 450 to 550 nm. In this median range, effective compositions are obtained when 10% of particles have a volume diameter of 260 nm or below and 90% of particles have a volume diameter of 1450 nm or below.

10

Using the milling beads and aqueous carrier system described above, a composition having the preferred particle size distribution may be obtained surprisingly quickly, for example after milling for about 30 minutes on a small scale mill using product recirculation. Increasing the milling time, for example to about 1 hour, enables the largest particles to be reduced so that at least 90% of particles have a volume diameter of less than 1000 nm. However, the effect on the median value is marginal so longer milling times are not cost effective. Similarly, for large scale processing, batch sizes of up to 200Kg for a compound loading of about 20% w/w, can be processed surprisingly quickly, with the preferred particle size distribution obtained after one pass of product over a 70 minute period.

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The aqueous dispersion obtained from the milling process may be used directly as a therapeutic agent if prepared under conditions of appropriate hygiene. Using water and other components which meet Ph Eur standards, compositions can be obtained which can be stored for up to one month at 5°C without bacterial growth being detected.

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However, for the preparation of formulations for use in human therapy, it is preferred that the aqueous dispersion is converted to a dried powder. This is carried out most suitably by spray drying, typically collecting the product from the dryer using a cyclone separator. By including the excipients mentioned above in the aqueous medium for milling, a powder composition containing the particulate compounds of Formula I and Formula II is obtainable as a composition which has good flowability and is suitable for incorporation into a tablet formulation or a powder formulation for capsules.

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Compounds of Formula I and II have hitherto been formed into tablets by first micronising the drug substance and then wet granulating the micronised drug with the tablet excipients. The spray dried powder produced in this invention can be formed into tablets by direct compression. Surprisingly it has been found that the milling time to

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achieve the desired particle size distribution is substantially the same whether the starting material is micronised or unmicronised. The ability to commence the bead milling with unmicronised drug substance as obtained from the primary manufacturing process makes the present milling process especially cost-effective. The wet cake from  
5 manufacture is washed and tray dried and is then ready for bead milling. Alternatively, for certain compounds it may be possible for the wet cake to be washed and resuspended ready for bead milling, thus eliminating an expensive drying stage.

The compounds of Formula I and II are believed to be useful in the treatment and/or  
10 prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's  
15 disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Gilles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially  
20 trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction and/or amyotrophic lateral sclerosis (ALS). The administration of such compounds in particulate form to a mammal may be by  
25 way of oral, parenteral, sub-lingual, nasal, pulmonary, rectal or transdermal administration.

An amount effective to treat the disorders hereinbefore described depends on the usual factors such as the nature and severity of the disorders being treated and the weight of  
30 the mammal. However, a unit dose will normally contain 1 to 1000 mg, suitably 1 to 500 mg, for example an amount in the range of from 2 to 400 mg such as 2, 5, 10, 20, 30, 40, 50, 100, 200, 300 and 400 mg of the active compound. Unit doses will normally be administered once or more than once per day, for example 1, 2, 3, 4, 5 or 6 times a day, more usually 1 to 4 times a day, such that the total daily dose is  
35 normally in the range, for a 70 kg adult of 1 to 1000 mg, for example 5 to 500 mg,

that is in the range of approximately 0.01 to 15 mg/kg/day, more usually 0.1 to 6 mg/kg/day, for example 1 to 6 mg/kg/day.

5 It is greatly preferred that the compound of Formula I is administered in the form of a unit-dose composition, such as a unit dose oral, including sub-lingual, nasal, pulmonary, rectal, topical or parenteral (especially intravenous) composition.

Such compositions are prepared by admixture and are suitably adapted for oral, parenteral or pulmonary administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable  
10 powders, injectable and infusable solutions or suspensions or respirable powders or powder suspensions or suppositories. Suitable apparatus for use in administration via the pulmonary route are described for example in US Patents Nos 5,363,842, 5,392,768, 5,394,866, 5,404,871, 5,497,763, 5,509,404, 5,544,646, and 5,608,647.  
15 Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tableting  
20 agents (compression aids), lubricants, disintegrants, colorants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents.  
25 Suitable disintegrants include starch, cross linked polyvinylpyrrolidone and other super disintegrants and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

These solid oral compositions may be prepared by conventional methods of blending, filling, tableting or the like. Repeated blending operations may be used to distribute  
30 the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily  
35 suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid

- preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.
- 10 Oral formulations also include conventional controlled release formulations, such as tablets or granules having an enteric coating or otherwise modified to control the release of the active compound for example by the inclusion of gel forming polymers such as Methocel K4M.
- 15 For parenteral administration, fluid unit dose forms are prepared containing the compound and a sterile vehicle. Parenteral suspensions are normally prepared by suspending the compound in a sterile vehicle, having first sterilized the compound by exposure to ethylene oxide, gamma irradiation or other sterilising process before suspending in the sterile vehicle. Alternatively, the entire process from the
- 20 recrystallisation of the active compound, the solution of which has previously been sterile filtered, for example through a 0.22 micron membrane filter, can be conducted under aseptic conditions to ensure sterility. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.
- 25 As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.
- Accordingly the present invention also provides a method of treatment and/or
- 30 prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's
- 35 disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive

compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Gilles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction and/or amyotrophic lateral sclerosis (ALS), comprising administering to the sufferer in need thereof an effective or prophylactic amount of a composition of this invention.

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In a further aspect the invention provides the use of a composition of this invention for the manufacture of a medicament for the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Gilles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction and/or amyotrophic lateral sclerosis (ALS).

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A preferred procedure for making a small scale particulate composition of this invention can be carried out using a two chamber bead mill, such as a laboratory scale machine, sold under the trade name DENA Mill by Dena Systems BK Ltd, Mapplewell, Barnsley, S75 6DT, with a milling capacity of 2 litres. The mill comprises two reaction chambers SPS 1, SPS 2, and three different reactors D3, S1 SS. The mill can be operated in three different modes, "process one", "process two" and "process one and two combined". Process one uses the SPS1 reaction chamber, which contains 1.25 mm beads. Process two uses the SPS 2 reaction chamber, which contains 0.4 mm beads. When the mill is run using process one and two combined the suspension of product to be milled passes through both reaction chambers.

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The reaction chambers SPS 1 and SPS2 contain rotating paddles and both the reaction chambers and paddles are manufactured from hard wearing, inert nylon. The inside of the discharge end of the reaction chambers are covered by a sieve of suitable size to stop the beads and any unmilled material leaving the chamber. The rotation speed of the paddles is constant.

The reactors D3, S1 and SS carry out different processes. The reactor D3 is a de-agglomerating reactor; it is designed mainly to de-agglomerate the substance being milled prior to entering the SPS 1 reaction chamber. The reactor S1 is a shearing and emulsifying reactor; it ensures a uniform suspension is produced at the end of the milling process. The SS reactor is designed to homogenise materials and emulsify where appropriate the suspension prior to exiting the mill. Suitable reactors for mixing and homogenizing solid suspensions are described in UK Patent No 2 268 090 B.

The interior of each reactor is a honeycomb baffle structure, arranged to produce angles of flow within the reactor dictated by the function of the reactor. The mill also has two heat exchangers; one for cooling the output of each reaction chamber.

When using this mill in the procedures of the present invention, the mill was operated in accordance with the manufacturer's instructions for "process one and process two combined", so that the compound to be milled was circulated between the two reaction chambers.

The mill chambers were loaded with YTZ® ceramic beads manufactured from yttria-stabilized, high purity zirconia powder (manufactured by Nikkato Corporation, Japan) as follows.

	Chamber	Beads	
30	SPS 1	Diameter	1.25mm <sup>±</sup> 0.15 mm
		Density	6.07 g/cm <sup>3</sup>
		Hardness	12.6Gpa.
		Weight	830 g
35	SPS 2	Diameter	0.4 mm + 0.1mm / -0.05mm
		Density	6.07 g/cm <sup>3</sup>

Hardness	12.5Gpa.
Weight	830 g

5 The milled suspension was spray dried using a Mobile Minor Spray Dryer, manufactured by Niro Ltd. Denmark. In this apparatus, the aqueous suspension from the mill is fed by pump into a drying chamber as an atomised spray. The dried powder passes into a cyclone separator from which powdered product is removed.

10 The Mobile Minor was operated in accordance with the manufacturers instructions at the following settings.

Machine Settings	Atomiser Speed	about 25,000 rpm
	Exhaust Fan/Heater	Setting II
	Pump Speed	40 rpm
15	Inlet Temperature	140°C
	Outlet Temperature	70°C

Suspensions for milling using the apparatus described above were prepared from:

Compound 1	SB Pharmaceuticals (in unmilled form, particle size typically 1mm)
Compound 2	As above
Mannitol	from Roquette UK Ltd
Hydroxypropyl Methylcellulose	from Stancourt Sons and Muir
Sodium Lauryl Sulphate	from Henkel Organics

5

The proportions of the compounds were varied as detailed below.

Suspensions were prepared by dispersing hydroxypropylmethylcellulose (HPMC) in purified water, using a suitable mixer. The mannitol was added to the hydroxypropyl methylcellulose dispersion, followed by the sodium lauryl sulphate. Then, while mixing at a high speed, the drug under test was dispersed and mixing continued until no drug agglomerates remained.

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The following formulations of suspension were investigated.

15	Component	Specification	Proportion % w/w					
		Formulation Number >	1	2	3	4	5	6
	Compound 1	SB Pharmaceuticals	20	15	10	20	30	40
		Specification						
	Mannitol	Ph Eur	10	7.5	5	5	5	5
20	HPMC	Ph Eur	1.5	1.5	1.5	1.5	1.5	1.5
	Sodium	Ph Eur	0.2	0.2	0.1	0.2	0.3	0.4
	Lauryl Sulphate							
	Purified Water	Ph Eur		to	to	to	to	to
	to							
25			100	100	100	100	100	100

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After milling the suspensions of Formulations 1 - 6, the results are reported as D(0.1), D(0.5), and D(0.9). D(0.1) represents the size (as volume diameter) below which 10% of the particles lie, D(0.5) is the size below which 50% of the particles lie, also known as the median. D(0.9) is the measurement below which 90% of the particles lie.



The particle size distribution was measured using a Malvern Mastersizer S laser diffraction unit from Malvern Instruments Ltd., Malvern, England.

### Suspension

- 5 Suspensions containing 10% w/w Compound 1, 15% w/w Compound 1, 20% w/w Compound 1 (Formulations 3, 2, 1) were milled successfully, reaching suitable product parameters within 60 minutes (see Tables 1, 2, 3). It was found that a 30% w/w suspension (Formulation 5) could be manufactured as a slurry but the bead mill could only process the slurry for a few minutes before the second reaction chamber, SPS 2  
10 (0.4mm beads), became blocked. A 40% w/w slurry (Formulation 6) could not be milled, as it would not suspend long enough for transfer to the mill reservoir.

**Table 1**

Time (Minutes)	Formulation 1		
	D(0.1) $\mu\text{m}$	D(0.5) $\mu\text{m}$	D(0.9) $\mu\text{m}$
0	ND	ND	ND (Unmicronised Drug)
60	0.24	0.40	0.71
120	0.27	0.39	0.56

20 ND - Not determined

**Table 2**

Time (Minutes)	Formulation 2		
	D(0.1) $\mu\text{m}$	D(0.5) $\mu\text{m}$	D(0.9) $\mu\text{m}$
0	0.53	10.21	73.06 (Micronised Drug)
60	0.25	0.40	0.68
120	0.27	0.40	0.57

**Table 3**

Time (Minutes)	Formulation 3		
	D(0.1) $\mu\text{m}$	D(0.5) $\mu\text{m}$	D(0.9) $\mu\text{m}$
0	35.59	112.12	417.34 (Unmicronised)
60	0.25	0.41	0.77
120	0.25	0.39	0.60

Milling of Formulation 1 was repeated with testing at shorter intervals, as shown in Table 4. Comparison with Table 1 shows that the desirable parameters are reached between 45 and 60 minutes of milling.

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**Table 4**

	Time (Minutes)	Formulation 1		
		D(0.1) $\mu\text{m}$	D(0.5) $\mu\text{m}$	D(0.9) $\mu\text{m}$
	15	0.33	1.40	7.38
10	25	0.28	0.68	2.52
	35	0.28	0.62	1.99
	45	0.27	0.60	1.93

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15 The suspension of Formulation 4 was milled for 70 minutes and samples analysed for particle size at 10 minute intervals (Table 5). It can be seen that a desirable particle size was achieved in 30 minutes milling time. After 30 minutes milling no more significant particle size reduction was achieved.

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**Table 5**

	Time (Minutes)	Formulation 4		
		D(0.1) $\mu\text{m}$	D(0.5) $\mu\text{m}$	D(0.9) $\mu\text{m}$
	0	27.27	85.96	343.72 (Unmicronised)
	10	0.27	0.58	1.66
25	20	0.27	0.54	1.54
	30	0.26	0.53	1.45
	50	0.26	0.48	1.26
	60	0.26	0.45	0.95
	70	0.25	0.44	0.93

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For all suspensions with a mannitol level of 5% to 10% spray drying was successful, as was the redispersion of the spray dried material.

35 To demonstrate that the process is reproducible, six batches (A - F) of 20kg of the suspension of Formulation 4 were milled in sub-lots of 2kg. Sixty lots were milled, and

particle size analysis was carried out on a sample of the 20kg bulk. For all the six 20kg lots the desirable particle size was achieved (Table 6) after 30 minutes milling time. The standard deviation for the three measurement areas is very low, showing no batch to batch variation.

5 (D(0.1)  $4 \times 10^{-3}$ , D(0.5)  $5.5 \times 10^{-3}$ , D(0.9)  $6 \times 10^{-3}$ .

**Table 6**

	Formulation	D(0.1) $\mu\text{m}$	D(0.5) $\mu\text{m}$	D(0.9) $\mu\text{m}$
	4 A	0.27	0.49	1.03
10	4 B	0.26	0.49	1.16
	4 C	0.26	0.50	1.23
	4 D	0.26	0.50	1.18
	4 E	0.26	0.50	1.21
	4 F	0.26	0.49	1.16

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A preferred procedure for making a commercial scale particulate composition of this invention may be carried out using a five chamber bead mill such as a commercial scale machine, sold under the trade name DENA DS-1P5 Mill by Dena Systems BK Ltd, Mapplewell, Barnsley, S75 6DT, with a milling capacity of 2 to 3 litres per minute. The mill comprises five reaction chambers SPS 1 to SPS 5, and seven different reactors (type D, S and SS). The mill is operated in one mode by passing product once through each of the mill chambers. Depending on the product, between one and five mill chambers can be used.

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The reaction chambers SPS 1 to SPS5 and the reactors are of similar design to the small scale mill referred to above

30 The mill chambers were loaded with YTZ® ceramic beads manufactured from yttria-stabilized, high purity zirconia powder (manufactured by Nikkato Corporation, Japan) as follows. Bead sizes range between 0.3mm and 1.25mm in diameter. Bead loadings in each chamber vary from 6250 cc to 6750cc

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The milled suspension was spray dried using a Niro Spray Dryer, manufactured by Niro Ltd, Denmark. In this apparatus, the aqueous suspension from the mill is fed by pump into a drying chamber as an atomised spray. The dried powder passes into a cyclone separator from which powdered product is removed.

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The spray drier was operated in accordance with the manufacturers instructions at the following settings.

10	Machine Settings	Atomiser Speed	21,000 to about 25,000 rpm
		Pump Speed	rpm
		Inlet Temperature	140°C
		Outlet Temperature	70°C

Suspensions for milling using the apparatus described above were prepared from identical excipients and active as outlined above for the small scale milling experiments:

The following formulations of suspension were investigated.

5	Component	Specification	Proportion % w/w
		Formulation Number >	1
	Compound 1	SB Pharmaceuticals	20
		Specification	
	Mannitol	Ph Eur	10
10	HPMC	Ph Eur	1.5
	Sodium	Ph Eur	0.2
	Lauryl Sulphate		
	Purified Water	Ph Eur	to
			100

15

After milling the suspensions of Formulation 1 using different mill chamber bead loadings and alternative bead sizes, the range of results are reported in Table 7 as D(0.1), D(0.5), and D(0.9). D(0.1) represents the size (as volume diameter) below which 10% of the particles lie, D(0.5) is the size below which 50% of the particles lie, also known as the median. D(0.9) is the measurement below which 90% of the particles lie.

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The particle size distribution was measured using a Malvern Mastersizer S laser diffraction unit from Malvern Instruments Ltd., Malvern, England.

## 25 Suspension

**Table 7**

30	Mill chamber	Formulation 1		
		D(0.1) $\mu\text{m}$	D(0.5) $\mu\text{m}$	D(0.9) $\mu\text{m}$
	0	36	112	417 (Unmicronised Drug)
	1	0.25 to 0.46	2.4 to 4.2	10.3 to 18
	2	0.32 to 0.34	1.1 to 1.3	5.0 to 6.5
	3	0.29 to 0.30	0.71 to 0.87	2.8 to 4.5
35	4	0.25 to 0.30	0.54 to 0.81	1.4 to 2.1
	5	0.25 to 0.28	0.48 to 0.52	1.0 to 1.3

The levels of yttrium and zirconium in all milled suspensions were assayed using inductively coupled plasma analysis and found to be at low and acceptable levels. The iron levels were also low. An acceptable level for zirconium was set at < 200ppm Zr, and yttrium 20ppm in the spray dried powder. The results show that the beads are not breaking down during the milling process and the nylon mill chambers are not being damaged by the beads or the suspension.

### Bio-Equivalence Study

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A bio-equivalence study to determine the relative bioavailability of four oral formulations of Compound 1 in healthy volunteers was performed.

The study design comprised an open, randomised, four part crossover. Each subject was to receive, randomly, on separate days, a single oral 400 mg dose of each of the four different formulations of Compound 1. Compound 1 was administered orally in tablet or capsule form. On each of the four dosing days subjects were to receive a single oral dose of Compound 1, with a washout of at least 6 days between doses. For each subject the four formulations were randomly allocated to each study session. Doses were administered orally with 200 mL water, following a standard breakfast. The spray dried product from the suspension of Formulation 4 was compressed into tablets by direct compression.

A control tablet formulation was as follows:

25	<b>Excipient</b>	<b>mg/tablet</b>
	Compound 1 (micronised)	400.00
	Sodium starch glycollate	24.00
	Microcrystalline cellulose Ph.Eur.	23.28
	Polyvinylpyrrolidone USP	9.60
30	Sodium lauryl sulphate BP	2.40
	Lactose (monohydrate) Ph.Eur.	18.48
	Magnesium stearate Ph.Eur.	2.40
	Purified water Ph.Eur.	q.s. (removed during processing)
35	<b>Total tablet weight</b>	<b>480.16</b>

The test conditions were the same for both formulations. The results (Tables 10 and 11) show an increase in blood levels of Compound 1 by approximately 3-fold when dosing with tablets of Formulation 4 when compared to the tablet sourced from micronised drug substance.

Table 10

	Control Tablet	Wet Milled Spray Dried Tablet
5		
AUC (mg.hr/ml)	11.8	31.5
C MAX. (mg/ml)	1.07	3.03
10		
tmax/hr	3.8	3.3

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AUC - Area under the curve

C MAX - Maximum plasma concentration

tmax - Time to maximum plasma level



**Table 11**  
**Results for Bio-equivalence study**

	Time	Control Tablet	Wet Milled Spray Dried Tablet
	(Hours)	(plasma concentration $\mu\text{g/ml}$ )	
5	0	0.00	0.00
	0.48	0.20	0.20
	1.0	0.35	0.65
10	1.5	0.50	1.30
	2.0	0.70	2.40
	3.0	1.00	2.75
	4.0	0.95	3.00
	6.0	0.90	2.30
15	8.0	0.69	1.75
	10.0	0.65	1.50
	12.0	0.60	1.30
	24.0	0.50	0.80

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#### **Rat maximal electroshock seizure threshold (MEST) test**

For full details see Upton *et al* (1997, *Br.J. Pharmacol.*, **121**, 1679-1686)

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The threshold for electroshock-induced tonic hindlimb extensor seizures in male rats (Sprague Dawley strain, 70-130g) was determined using a Hugo Sachs Elektronik stimulator which delivered a constant current (0.3 s duration, 50 Hz, sinewave form, fully adjustable between 1-300 mA) via corneal electrodes. The stimulus intensity was varied (from the typical baseline current of 25 mA) by an "up-and-down" method of shock titration using current steps of 5-20 mA. Hindlimb extension was scored as absent or present. The data generated from treatment groups of 10-14 rats were used to calculate the  $\text{CC}_{50}$  value (current producing maximal seizures of 50% of animals)  $\pm$  s.e.m. according to the method of Kimball *et al* (1957, *Radiation Res.* **7**, 1-12). The effects of the various drug treatments were expressed as the % change in  $\text{CC}_{50}$  values compared to vehicle-treated control levels. An increase in seizure threshold is indicative

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of an anticonvulsant effect. Significant effects ( $P < 0.05$ ) of drugs on the threshold for maximal electroshock seizures were determined by comparison of the potency ratios of the  $CC_{50}$  values of the drug and vehicle-treated groups by the method of Litchfield and Wilcoxon (1949, *J. Pharmacol. Exp. Ther.* 96, 99-113).

5

Test drugs were administered orally by gavage using a dose volume of 1 ml/kg.

#### Anticonvulsant Effect of Different Formulations of Compound 2 (5 mg/kg p.o.) in the Rat MEST Test

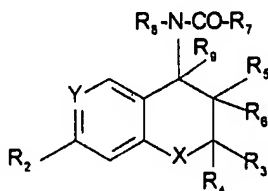
10

	Pre-Test Time (mins)	% Increase in Seizure Threshold				
		1% methyl cellulose	micronised <sup>a</sup>	wet-milled <sup>b</sup> + SLS	wet -milled <sup>c</sup>	formulation 4 <sup>d</sup>
15	15	76	114	181	182	184
	30	202	231	369	335	410
	60	194	369	444	424	492
	90	-	549	557	410	580
	120	576	798	526	839	893
20	15 min/2hr	11%	14%	34%	22%	21%

- Conclusions:
1. c and d have better overall effect than a
  2. b, c & d have faster rate of onset than a

## CLAIMS:

1. A pharmaceutical composition comprising a compound of Formula I or Formula II below in particulate form, said composition having a particle size distribution such  
 5 that the median value of the volume mean diameter is within the range of from 350 to 700 nm:



I

wherein:

10

either Y is N and R<sub>2</sub> is hydrogen, or Y is C-R<sub>1</sub>

where:

- 15 either one of R<sub>1</sub> and R<sub>2</sub> is hydrogen and the other is selected from the class of hydrogen, C<sub>3-8</sub> cycloalkyl, C<sub>1-6</sub> alkyl optionally interrupted by oxygen or substituted by hydroxy, C<sub>1-6</sub> alkoxy or substituted aminocarbonyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxycarbonyl, C<sub>1-6</sub> alkylcarbonyloxy, C<sub>1-6</sub> alkoxy, nitro, cyano, halo, trifluoromethyl, CF<sub>3</sub>S, or a group CF<sub>3</sub>-A-, where A is -CF<sub>2</sub>-, -CO-, -CH<sub>2</sub>- or  
 20 CH(OH), trifluoromethoxy, C<sub>1-6</sub> alkylsulphinyl, C<sub>1-6</sub> alkylsulphonyl, C<sub>1-6</sub> alkoxy-sulphinyl, C<sub>1-6</sub> alkoxy-sulphonyl, aryl, heteroaryl, arylcarbonyl, heteroarylcarbonyl, arylsulphinyl, heteroarylsulphinyl, arylsulphonyl, heteroarylsulphonyl in which any aromatic moiety is optionally substituted, C<sub>1-6</sub> alkylcarbonylamino, C<sub>1-6</sub> alkoxycarbonylamino, C<sub>1-6</sub> alkyl-thiocarbonyl, C<sub>1-6</sub> alkoxy-thiocarbonyl, C<sub>1-6</sub> alkyl-thiocarbonyloxy, 1-mercapto C<sub>2-7</sub> alkyl, formyl, or  
 25 aminosulphinyl, aminosulphonyl or aminocarbonyl, any amino moiety being optionally substituted by one or two C<sub>1-6</sub> alkyl groups, or C<sub>1-6</sub> alkylsulphinylamino, C<sub>1-6</sub> alkylsulphonylamino, C<sub>1-6</sub> alkoxy-sulphinylamino or C<sub>1-6</sub> alkoxy-sulphonylamino, or ethylenyl terminally substituted by C<sub>1-6</sub> alkylcarbonyl, nitro or cyano, or -C(C<sub>1-6</sub> alkyl)NOH or -C(C<sub>1-6</sub> alkyl)NNH<sub>2</sub>, or one of R<sub>1</sub> and R<sub>2</sub>  
 30 is nitro, cyano or C<sub>1-3</sub> alkylcarbonyl and the other is methoxy or amino optionally substituted by one or two C<sub>1-6</sub> alkyl or by C<sub>2-7</sub> alkanoyl;

5 R<sub>5</sub> is C<sub>1-6</sub> alkylcarbonyloxy, benzyloxy, ONO<sub>2</sub>, benzyloxy, phenoxy or C<sub>1-6</sub> alkoxy and R<sub>6</sub> and R<sub>9</sub> are hydrogen or R<sub>5</sub> is hydroxy and R<sub>6</sub> is hydrogen or C<sub>1-2</sub> alkyl and R<sub>9</sub> is hydrogen;

10  $R_8$  is hydrogen or  $C_{1-6}$  alkyl;

and X is oxygen or NR<sub>10</sub> where R<sub>10</sub> is hydrogen or C<sub>1-6</sub> alkyl;

R2C1=CC(=C(C=C1)C2)C3(C(C3)C4(C(C(C4)C5(C(C(C5)C6(C(C(C6)C7(C(C(C7)C8(C(C(C8)C9(C(C(C9)C10(C(C(C10)C11(C(C(C11)C12(C(C(C12)C13(C(C(C13)C14(C(C(C14)C15(C(C(C15)C16(C(C(C16)C17(C(C(C17)C18(C(C(C18)C19(C(C(C19)C20(C(C(C20)C21(C(C(C21)C22(C(C(C22)C23(C(C(C23)C24(C(C(C24)C25(C(C(C25)C26(C(C(C26)C27(C(C(C27)C28(C(C(C28)C29(C(C(C29)C30(C(C(C30)C31(C(C(C31)C32(C(C(C32)C33(C(C(C33)C34(C(C(C34)C35(C(C(C35)C36(C(C(C36)C37(C(C(C37)C38(C(C(C38)C39(C(C(C39)C40(C(C(C40)C41(C(C(C41)C42(C(C(C42)C43(C(C(C43)C44(C(C(C44)C45(C(C(C45)C46(C(C(C46)C47(C(C(C47)C48(C(C(C48)C49(C(C(C49)C50(C(C(C50)C51(C(C(C51)C52(C(C(C52)C53(C(C(C53)C54(C(C(C54)C55(C(C(C55)C56(C(C(C56)C57(C(C(C57)C58(C(C(C58)C59(C(C(C59)C60(C(C(C60)C61(C(C(C61)C62(C(C(C62)C63(C(C(C63)C64(C(C(C64)C65(C(C(C65)C66(C(C(C66)C67(C(C(C67)C68(C(C(C68)C69(C(C(C69)C70(C(C(C70)C71(C(C(C71)C72(C(C(C72)C73(C(C(C73)C74(C(C(C74)C75(C(C(C75)C76(C(C(C76)C77(C(C(C77)C78(C(C(C78)C79(C(C(C79)C80(C(C(C80)C81(C(C(C81)C82(C(C(C82)C83(C(C(C83)C84(C(C(C84)C85(C(C(C85)C86(C(C(C86)C87(C(C(C87)C88(C(C(C88)C89(C(C(C89)C90(C(C(C90)C91(C(C(C91)C92(C(C(C92)C93(C(C(C93)C94(C(C(C94)C95(C(C(C95)C96(C(C(C96)C97(C(C(C97)C98(C(C(C98)C99(C(C(C99)C100(C(C(C100)C101(C(C(C101)C102(C(C(C102)C103(C(C(C103)C104(C(C(C104)C105(C(C(C105)C106(C(C(C106)C107(C(C(C107)C108(C(C(C108)C109(C(C(C109)C110(C(C(C110)C111(C(C(C111)C112(C(C(C112)C113(C(C(C113)C114(C(C(C114)C115(C(C(C115)C116(C(C(C116)C117(C(C(C117)C118(C(C(C118)C119(C(C(C119)C120(C(C(C120)C121(C(C(C121)C122(C(C(C122)C123(C(C(C123)C124(C(C(C124)C125(C(C(C125)C126(C(C(C126)C127(C(C(C127)C128(C(C(C128)C129(C(C(C129)C130(C(C(C130)C131(C(C(C131)C132(C(C(C132)C133(C(C(C133)C134(C(C(C134)C135(C(C(C135)C136(C(C(C136)C137(C(C(C137)C138(C(C(C138)C139(C(C(C139)C140(C(C(C140)C141(C(C(C141)C142(C(C(C142)C143(C(C(C143)C144(C(C(C144)C145(C(C(C145)C146(C(C(C146)C147(C(C(C147)C148(C(C(C148)C149(C(C(C149)C150(C(C(C150)C151(C(C(C151)C152(C(C(C152)C153(C(C(C153)C154(C(C(C154)C155(C(C(C155)C156(C(C(C156)C157(C(C(C157)C158(C(C(C158)C159(C(C(C159)C160(C(C(C160)C161(C(C(C161)C162(C(C(C162)C163(C(C(C163)C164(C(C(C164)C165(C(C(C165)C166(C(C(C166)C167(C(C(C167)C168(C(C(C168)C169(C(C(C169)C170(C(C(C170)C171(C(C(C171)C172(C(C(C172)C173(C(C(C173)C174(C(C(C174)C175(C(C(C175)C176(C(C(C176)C177(C(C(C177)C178(C(C(C178)C179(C(C(C179)C180(C(C(C180)C181(C(C(C181)C182(C(C(C182)C183(C(C(C183)C184(C(C(C184)C185(C(C(C185)C186(C(C(C186)C187(C(C(C187)C188(C(C(C188)C189(C(C(C189)C190(C(C(C190)C191(C(C(C191)C192(C(C(C192)C193(C(C(C193)C194(C(C(C194)C195(C(C(C195)C196(C(C(C196)C197(C(C(C197)C198(C(C(C198)C199(C(C(C199)C200(C(C(C200)C201(C(C(C201)C202(C(C(C202)C203(C(C(C203)C204(C(C(C204)C205(C(C(C205)C206(C(C(C206)C207(C(C(C207)C208(C(C(C208)C209(C(C(C209)C210(C(C(C210)C211(C(C(C211)C212(C(C(C212)C213(C(C(C213)C214(C(C(C214)C215(C(C(C215)C216(C(C(C216)C217(C(C(C217)C218(C(C(C218)C219(C(C(C219)C220(C(C(C220)C221(C(C(C221)C222(C(C(C222)C223(C(C(C223)C224(C(C(C224)C225(C(C(C225)C226(C(C(C226)C227(C(C(C227)C228(C(C(C228)C229(C(C(C229)C230(C(C(C230)C231(C(C(C231)C232(C(C(C232)C233(C(C(C233)C234(C(C(C234)C235(C(C(C235)C236(C(C(C236)C237(C(C(C237)C238(C(C(C238)C239(C(C(C239)C240(C(C(C240)C241(C(C(C241)C242(C(C(C242)C243(C(C(C243)C244(C(C(C244)C245(C(C(C245)C246(C(C(C246)C247(C(C(C247)C248(C(C(C248)C249(C(C(C249)C250(C(C(C250)C251(C(C(C251)C252(C(C(C252)C253(C(C(C253)C254(C(C(C254)C255(C(C(C255)C256(C(C(C256)C257(C(C(C257)C258(C(C(C258)C259(C(C(C259)C260(C(C(C260)C261(C(C(C261)C262(C(C(C262)C263(C(C(C263)C264(C(C(C264)C265(C(C(C265)C266(C(C(C266)C267(C(C(C267)C268(C(C(C268)C269(C(C(C269)C270(C(C(C270)C271(C(C(C271)C272(C(C(C272)C273(C(C(C273)C274(C(C(C274)C275(C(C(C275)C276(C(C(C276)C277(C(C(C277)C278(C(C(C278)C279(C(C(C279)C280(C(C(C280)C281(C(C(C281)C282(C(C(C282)C283(C(C(C283)C284(C(C(C284)C285(C(C(C285)C286(C(C(C286)C287(C(C(C287)C288(C(C(C288)C289(C(C(C289)C290(C(C(C290)C291(C(C(C291)C292(C(C(C292)C293(C(C(C293)C294(C(C(C294)C295(C(C(C295)C296(C(C(C296)C297(C(C(C297)C298(C(C(C298)C299(C(C(C299)C300(C(C(C300)C301(C(C(C301)C302(C(C(C302)C303(C(C(C303)C304(C(C(C304)C305(C(C(C305)C306(C(C(C306)C307(C(C(C307)C308(C(C(C308)C309(C(C(C309)C310(C(C(C310)C311(C(C(C311)C312(C(C(C312)C313(C(C(C313)C314(C(C(C314)C315(C(C(C315)C316(C(C(C316)C317(C(C(C317)C318(C(C(C318)C319(C(C(C319)C320(C(C(C320)C321(C(C(C321)C322(C(C(C322)C323(C(C(C323)C324(C(C(C324)C325(C(C(C325)C326(C(C(C326)C327(C(C(C327)C328(C(C(C328)C329(C(C(C329)C330(C(C(C330)C331(C(C(C331)C332(C(C(C332)C333(C(C(C333)C334(C(C(C334)C335(C(C(C335)C336(C(C(C336)C337(C(C(C337)C338(C(C(C338)C339(C(C(C339)C340(C(C(C340)C341(C(C(C341)C342(C(C(C342)C343(C(C(C343)C344(C(C(C344)C345(C(C(C345)C346(C(C(C346)C347(C(C(C347)C348(C(C(C348)C349(C(C(C349)C350(C(C(C350)C351(C(C(C351)C352(C(C(C352)C353(C(C(C353)C354(C(C(C354)C355(C(C(C355)C356(C(C(C356)C357(C(C(C357)C358(C(C(C358)C359(C(C(C359)C360(C(C(C360)C361(C(C(C361)C362(C(C(C362)C363(C(C(C363)C364(C(C(C364)C365(C(C(C365)C366(C(C(C366)C367(C(C(C367)C368(C(C(C368)C369(C(C(C369)C370(C(C(C370)C371(C(C(C371)C372(C(C(C372)C373(C(C(C3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II

20 either Y is N and R<sub>2</sub> is hydrogen, or Y is C-R<sub>1</sub>

either one of R<sub>1</sub> and R<sub>2</sub> is hydrogen and the other is selected from the class of hydrogen, C<sub>3-8</sub> cycloalkyl, C<sub>1-6</sub> alkyl optionally interrupted by oxygen or substituted by hydroxy, C<sub>1-6</sub> alkoxy or substituted aminocarbonyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxycarbonyl, C<sub>1-6</sub> alkylcarbonyloxy, C<sub>1-6</sub> alkoxy, nitro, cyano, halo, trifluoromethyl, CF<sub>3</sub>S, or a group CF<sub>3</sub>-A-, where A is -CF<sub>2</sub>-, -CO-, -CH<sub>2</sub>-, CH(OH), SO<sub>2</sub>, SO, CH<sub>2</sub>-O, or CONH, or a group CF<sub>2</sub>H-A'- where A' is oxygen, sulphur, SO, SO<sub>2</sub>, CF<sub>2</sub> or CFH; trifluoromethoxy, C<sub>1-6</sub> alkylsulphinyl, perfluoro C<sub>2-6</sub> alkylsulphonyl, C<sub>1-6</sub> alkylsulphonyl, C<sub>1-6</sub> alkoxysulphinyl, C<sub>1-6</sub> alkoxysulphonyl,

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- alkoxy-thiocarbonyl, C<sub>1-6</sub> alkyl-thiocarbonyloxy, 1-mercapto C<sub>2-7</sub> alkyl, formyl, or aminosulphinyl, aminosulphonyl or aminocarbonyl, any amino moiety being optionally substituted by one or two C<sub>1-6</sub> alkyl groups, or C<sub>1-6</sub> alkylsulphinylamino, C<sub>1-6</sub> alkylsulphonylamino, C<sub>1-6</sub> alkoxyulphinylamino or C<sub>1-6</sub> alkoxyulphonylamino, or ethylenyl terminally substituted by C<sub>1-6</sub> alkylcarbonyl, nitro or cyano, or -C(C<sub>1-6</sub> alkyl)NOH or -C(C<sub>1-6</sub> alkyl)NNH<sub>2</sub>, or one of R<sub>1</sub> and R<sub>2</sub> is nitro, cyano or C<sub>1-3</sub> alkylcarbonyl and the other is methoxy or amino optionally substituted by one or two C<sub>1-6</sub> alkyl or by C<sub>2-7</sub> alkanoyl; or R<sub>1</sub> and R<sub>2</sub> together are - (CH<sub>2</sub>)<sub>4</sub>- or -CH = CH-CH = CH-, or form an optionally substituted triazole or
- 10 oxadiazole ring;
- one of R<sub>3</sub> and R<sub>4</sub> is hydrogen or C<sub>1-4</sub> alkyl and the other is C<sub>1-4</sub> alkyl, CF<sub>3</sub> or CH<sub>2</sub> X<sup>a</sup> where X<sup>a</sup> is fluoro, chloro, bromo, iodo, C<sub>1-4</sub> alkoxy, hydroxy, C<sub>1-4</sub> alkylcarbonyloxy, -S-C<sub>1-4</sub> alkyl, nitro, amino optionally substituted by one or two
- 15 C<sub>1-4</sub> alkyl groups; cyano or C<sub>1-4</sub> alkoxy carbonyl or R<sub>3</sub> and R<sub>4</sub> together are C<sub>2-5</sub> polymethylene optionally substituted by C<sub>1-4</sub> alkyl;
- R<sub>5</sub> is C<sub>1-6</sub> alkylcarbonyloxy, benzoyloxy, ONO<sub>2</sub>, benzyloxy, phenyloxy or C<sub>1-6</sub> alkoxy and R<sub>6</sub> and R<sub>9</sub> are hydrogen or R<sub>5</sub> is hydroxy and R<sub>6</sub> is hydrogen or C<sub>1-2</sub> alkyl and R<sub>9</sub> is hydrogen;
- 20 R<sub>7</sub> is heteroaryl or phenyl; both of which are optionally substituted one or more times independently with a group or atom selected from chloro, fluoro, bromo, iodo, nitro, amino optionally substituted once or twice by C<sub>1-4</sub> alkyl, cyano, azido, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, trifluoromethoxy and trifluoromethyl;
- 25 R<sub>8</sub> is hydrogen; C<sub>1-6</sub> alkyl, OR<sub>9</sub> or NHCOR<sub>10</sub> wherein R<sub>9</sub> is hydrogen, C<sub>1-6</sub> alkyl, formyl, C<sub>1-6</sub> alkanoyl, aroyl or aryl-C<sub>1-6</sub> alkyl and R<sub>10</sub> is hydrogen, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, mono or di C<sub>1-6</sub> alkyl amino, amino, amino-C<sub>1-6</sub> alkyl, hydroxy-C<sub>1-6</sub> alkyl, halo-C<sub>1-6</sub> alkyl, C<sub>1-6</sub> acyloxy-C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy carbonyl-C<sub>1-6</sub> alkyl, aryl or heteroaryl;
- the R<sub>8</sub>-N-CO-R<sub>7</sub> group being *cis* to the R<sub>5</sub> group;
- 35 and X is oxygen or NR<sub>10</sub> where R<sub>10</sub> is hydrogen or C<sub>1-6</sub> alkyl.

2. A composition according to claim 1 in which the particles of the compounds of Formula I or Formula II are present as a monomodal distribution.
3. A composition according to claim 2 in which no more than 10% of the particles  
5 having a volume diameter of 280 nm or below, and no less than 90% of the particles having a volume diameter of 2000 nm or below.
4. A composition according to any one of claims 1 to 3 in which the median  
10 volume diameter is in the range of 450 to 550 nm.
5. A composition according to claim 4 in which 10% of particles have a volume diameter of 260 nm or below and 90% of particles have a volume diameter of 1450 nm or below.
- 15 6. A composition according to any one of claims 1 to 6 which is obtainable by wet milling compounds of Formula I and Formula II as an aqueous dispersion.
7. A composition according to claim 6 which is obtainable by wet milling using a multi-chamber bead mill with single pass or recirculation of product between the  
20 chambers.
8. A composition according to claim 6 or 7 which is obtainable using ceramic beads of rare earth oxides as milling medium.
- 25 9. A composition according to claim 7 or 8 which is obtainable using a multichamber chamber mill in which the beads in one chamber are of a smaller diameter than the beads in the other chambers.
10. A composition according to claim 9 which is obtainable by using a range of bead  
30 sizes between 0.4mm and 1.25mm in each chamber
11. A composition according to any one of claims 1 to 10 including a soluble carrier suitable as an excipient for spray drying.
12. A composition according to claim 10 in which the soluble carrier is mannitol.  
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13. A composition according to any one of claims 1 to 12 including a surfactant to maintain the particles in suspension during milling and on re-suspension.
14. A composition according to claim 13 in which the surfactant is sodium lauryl sulphate.
15. A composition according to any one of claims 1 to 14 including an anti-agglomeration agent effective after administration of a pharmaceutical formulation to a patient.
16. A composition according to claim 15 in which the anti-agglomeration agent is hydroxypropyl methyl cellulose.
17. A process for preparing a particulate composition of a sparingly water-soluble drug substance which comprises wet milling the drug substance as an aqueous dispersion in a multi-chamber bead mill with circulation of product between the chambers, the aqueous dispersion including a soluble carrier suitable as an excipient for spray drying, a surfactant to maintain the particles in suspension on re-suspension, and an anti-agglomeration agent effective after administration of a pharmaceutical formulation to a patient, and spray drying the aqueous dispersion after milling.
18. A process according to claim 17 in which the drug substance is a compound of Formula I or Formula II.
19. A process according to claim 18 in which the aqueous dispersion to be milled comprises about 10 to 30% w/w of a compound of Formula I or II, about 4 to 15% w/w of the soluble carrier, about 0.1 to 0.4% w/w of surfactant, and about 1% w/w to 2% w/w of the anti-agglomeration agent.
20. A method of treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntingdon's chorea, schizophrenia, obsessive

compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Gilles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction and/or amyotrophic lateral sclerosis (ALS) comprising administering to the sufferer in need thereof an effective or prophylactic amount of a composition according to any one of claims 1 to 16.

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21. The use of a composition according to any one of claims 1 to 16 for the manufacture of a medicament for the treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntington's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g. Gilles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity), temporomandibular joint dysfunction and/or amyotrophic lateral sclerosis (ALS).

22. A method of treatment and/or prophylaxis of anxiety, mania, depression, panic disorders and/or aggression, disorders associated with a subarachnoid haemorrhage or neural shock, the effects associated with withdrawal from substances of abuse such as cocaine, nicotine, alcohol and benzodiazepines, disorders treatable and/or preventable with anti-convulsive agents, such as epilepsy including post-traumatic epilepsy, Parkinson's disease, psychosis, migraine, cerebral ischaemia, Alzheimer's disease and other degenerative diseases such as Huntington's chorea, schizophrenia, obsessive compulsive disorders (OCD), neurological deficits associated with AIDS, sleep disorders (including circadian rhythm disorders, insomnia & narcolepsy), tics (e.g.

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- Giles de la Tourette's syndrome), traumatic brain injury, tinnitus, neuralgia, especially trigeminal neuralgia, neuropathic pain, dental pain, cancer pain, inappropriate neuronal activity resulting in neurodysthesias in diseases such as diabetes, multiple sclerosis (MS) and motor neurone disease, ataxias, muscular rigidity (spasticity),
- 5 temporomandibular joint dysfunction and/or amyotrophic lateral sclerosis (ALS), which comprises administering to a patient in need thereof an effective amount of a compound of Formula I or II, or a pharmaceutically acceptable salt or solvate thereof, and, optionally, a pharmaceutically acceptable carrier.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/08156

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/14 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 13657 A (SMITHKLINE BEECHAM PLC ;SMITHKLINE BEECHAM CORP (US); CHAN WAI NGO) 23 June 1994 cited in the application see page 1, line 34 - page 5, line 8 see page 6, line 30 - page 7, line 36 see page 8, line 9-17 see claims ---	1-16, 18-22
A	WO 95 34545 A (SMITHKLINE BEECHAM PLC ;CHAN WAI NGOR (GB); MORGAN HELEN KATE ANN) 21 December 1995 cited in the application see page 1, line 30 - page 5, line 18 see examples 4,17 see claims --- -/-	1-16, 18-22

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/08156

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>US 5 518 738 A (EICKHOFF W MARK ET AL) 21 May 1996</p> <p>see column 2, line 41-61 see column 3, line 44-64 see column 4, line 53-67 see column 5, line 45-65 see claims</p> <p>---</p>	<p>1,4-6,8, 11-14, 17-19</p>
A	<p>EP 0 499 299 A (STERLING WINTHROP INC) 19 August 1992 cited in the application see page 2, line 50-52 see page 3, line 30-38 see page 4, line 16-31 see page 5, line 26-41 see examples 1,9 see page 11, line 25-26 see claims</p> <p>---</p>	<p>1,4-6,8, 13,17-19</p>
A	<p>US 5 534 270 A (DE CASTRO LAN) 9 July 1996</p> <p>see column 2, line 33-42 see column 3, line 3-16 see column 3, line 22-26 see column 4, line 29-44 see column 5, line 7-27 see claims</p> <p>-----</p>	<p>1,4-6,8, 13,17-19</p>

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/08156

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9413657 A	23-06-1994	AU 679955 B	17-07-1997
		AU 5655894 A	04-07-1994
		CA 2151507 A	23-06-1994
		EP 0673374 A	27-09-1995
		JP 11500405 T	12-01-1999
		MX 9307791 A	31-01-1995
		NZ 258611 A	27-07-1997
		SG 49907 A	15-06-1998
		ZA 9309239 A	14-10-1994
		CN 1094722 A	09-11-1994
WO 9534545 A	21-12-1995	AU 701060 B	21-01-1999
		AU 2672795 A	05-01-1996
		AU 9614798 A	04-03-1999
		BG 101040 A	29-08-1997
		BR 9507980 A	12-08-1997
		CA 2192480 A	21-12-1995
		CZ 9603617 A	13-08-1997
		EP 0764157 A	26-03-1997
		FI 964936 A	06-02-1997
		HU 76136 A	30-06-1997
		JP 10501251 T	03-02-1998
		NO 965260 A	06-02-1997
		NZ 287872 A	27-05-1998
		PL 317579 A	14-04-1997
		SK 158796 A	09-07-1997
		US 5760074 A	02-06-1998
		ZA 9504732 A	06-05-1996
US 5518738 A	21-05-1996	AT 174506 T	15-01-1999
		AU 4900996 A	27-08-1996
		CA 2212779 A	15-08-1996
		DE 69601158 D	28-01-1999
		EP 0808156 A	26-11-1997
		ES 2125099 T	16-02-1999
		JP 10513198 T	15-12-1998
		WO 9624339 A	15-08-1996
EP 0499299 A	19-08-1992	US 5145684 A	08-09-1992
		AU 642066 B	07-10-1993
		AU 1014592 A	30-07-1992
		AU 654836 B	24-11-1994
		AU 1014792 A	30-07-1992
		CA 2059431 A	26-07-1992
		CA 2059432 A	26-07-1992
		EP 0498482 A	12-08-1992
		FI 920321 A	26-07-1992
		FI 920322 A	26-07-1992
		IL 100754 A	16-10-1996
		IL 100755 A	08-12-1995
		JP 4317053 A	09-11-1992
		JP 4295420 A	20-10-1992
		MX 9200291 A	01-10-1992
		MX 9200292 A	01-10-1992
		NO 303668 B	17-08-1998
		SG 55104 A	21-12-1998
		RU 2074002 C	27-02-1997
		RU 2066553 C	20-09-1996

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/08156

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0499299 A		US 5451393 A	19-09-1995
		US 5494683 A	27-02-1996
		US 5552160 A	03-09-1996
		US 5399363 A	21-03-1995
		US 5318767 A	07-06-1994
<hr/>			
US 5534270 A	09-07-1996	AU 4913196 A	27-08-1996
		WO 9624340 A	15-08-1996
<hr/>			